Electromechanical interrelations during dobutamine stress in normal subjects and patients with coronary artery disease: comparison of changes in activation and inotropic state

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Abstract

Objective—To identify the effects of altered ventricular activation during dobutamine stress on left ventricular function in normal subjects and in patients with coronary artery disease, and to distinguish these from an inotropic response.

Design—Prospective analysis of 12 lead ECG and echocardiogram at rest and at peak stress.

Setting—Tertiary referral centre for cardiac disease equipped with non-invasive facilities for pharmacological stress testing.

Methods—22 patients with coronary artery disease were compared with 17 age matched controls. Left ventricular ejection and filling patterns were assessed using Doppler echocardiography. Activation effects were correlated with relative left ventricular ejection and filling times, and the Z ratio ([left ventricular ejection + filling times]/RR interval). Inotropic response was measured from peak aortic acceleration.

Results—In controls, QRS shortened (by 4 ms, $p < 0.001$), and total ejection and filling periods lengthened (by 2 s/min, $p < 0.01$ and 5 s/min, $p < 0.001$, respectively). The Z ratio thus increased and correlated with QRS shortening ($r^2 = 0.69$). Peak aortic acceleration (PAA) increased by 135%, $p < 0.001$. In patients, QRS lengthened at peak stress (by 9 ms, $p < 0.001$). Total ejection and filling times did not change, but Z ratio fell, correlating with QRS prolongation ($r^2 = 0.65$). Nevertheless, PAA increased by 63%, $p < 0.001$.

Conclusions—Relative ejection and filling times reflect ventricular activation at rest and during stress independent of changes in inotropic state. By contrast, peak aortic acceleration reflects the positive inotropic effect of dobutamine on the myocardium, regardless of changes in activation.

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Keywords: stress echocardiography; ventricular activation; Z ratio; aortic acceleration

In 1926, Wiggers[1] suggested the importance of ventricular activation in determining the dynamics of ventricular contraction. More recent studies using dobutamine stress[2] have shown that the QRS duration becomes shorter in normal subjects as heart rate increases, but consistently prolongs in patients with coronary artery disease. In the present study, we aimed to determine whether these stress induced activation changes have predictable mechanical consequences as heart rate increases, and whether these can be dissociated from changes reflecting an altered left ventricular inotropic state.

Methods

Twenty two patients with suspected coronary artery disease were referred to our hospital for stress echocardiography to assess possible segmental wall motion abnormalities (for clinical details see table 1). Echocardiography was undertaken with the operator blind to the results of concurrent diagnostic tests for coronary artery disease (cardiac catheterisation, exercise electrocardiography, and thallium perfusion scanning). All patients had normal left ventricular cavity size and systolic function (defined as echocardiographic dimensions within the upper 95% confidence intervals of normal—that is, end diastolic dimension less than 5.6 cm and end systolic dimension less than 4.0 cm). No patient had valve disease or had experienced an acute ischaemic event in the seven days before the study. Patients in atrial fibrillation or with multiple ventricular ectopic beats at rest were excluded. The results were compared with 17 control subjects of similar age (table 1).

The protocol was approved by the Royal Brompton and Harefield ethics committee. All patients gave written informed consent.

DOBUTAMINE INFUSION PROTOCOL

Patients and controls were studied at rest and during dobutamine stress. Dobutamine was given by infusion pump at a starting rate of 5 μg/kg/min, with increments of 5 μg/kg/min every three minutes to a maximum dose of 40 μg/kg/min. Each increment corresponded to one stage of the test. Systolic and diastolic blood pressures were recorded at the end of each stage using a Critikon Dinamap monitor (Critikon Inc, Tampa, Florida, USA). Predetermined stress end points for controls were either the achievement of 85% predicted target heart rate (220 minus age in years (beats/min)) or the end of stage 8 of the dobutamine protocol. In patients, 1 mm ST segment shift (elevation or depression), T wave inversion, development of chest pain or shortness of breath, or a

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Table 1 Clinical details

Variable	*Controls (n=17)*	*Coronary artery disease (n=22)*
Age (years)	58 (11)	63 (10)
Male:female	5:12	13:9
EDD (cm)	5.0 (0.4)	4.9 (0.5)
ESD (cm)	3.3 (0.5)	3.3 (0.5)
FS (%)	34 (7)	32 (7)
Evidence for coronary heart disease		
3 vessel disease at cardiac catheterisation	–	17
2 vessel disease at cardiac catheterisation	–	5
Positive exercise test	–	19
Positive thallium	–	3
Clinical details		
Myocardial infarction	–	8
Effort induced angina	–	20
Diabetes	–	5
Hypertension	–	6
Smokers (ex or current)	–	12
Drug treatment		
Diuretics	–	1
Nitrates	–	13
β Blocker	–	3
ACE inhibitor	–	6

Values are mean (SD) or n.
ACE, angiotensin converting enzyme; EDD, end diastolic dimension; ESD, end systolic dimension; FS, fractional shortening.

20 mm Hg drop in systolic blood pressure were also used as stress end points.

ELECTROCARDIOGRAM

A standard 12 lead ECG was recorded at rest and at the end of each stage of dobutamine stress using a Hewlett-Packard Pagewriter Xli, with a built in analysis package (Hewlett-Packard Inc, Andover, Massachusetts, USA). ECG intervals were measured automatically and registered on a printed chart at a speed of 25 mm/s. The frequency response of the machine was 0.05–150 Hz with the baseline filter (0.4 Hz) inactivated.

DOPPLER ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed using a Hewlett Packard Sonos 5500 echocardiograph and a 2.5 MHz transducer. With the subject at rest in the semilateral position, cross sectional imaging in the left parasternal long axis plane was used to guide M mode recordings of the left ventricular minor axis (with the cursor at the tips of the mitral leaflets), the mitral leaflets themselves, and the aortic root. Diastolic forward flow across the mitral valve was recorded using pulsed wave Doppler obtained from the apical four chamber view, and aortic flow was obtained from the apical five chamber view with the sample volume placed at the tips of the respective valve leaflets. Rest and peak recordings were obtained at a paper speed of 100 mm/s, with a superimposed ECG (lead II) and phonocardiogram.

MEASUREMENTS

Electrocardiogram

Heart rate and QRS duration were measured at rest and at peak stress using inbuilt software. ST segment shift was measured manually in the lead showing the most change, 80 ms after the J point of the ST segment.

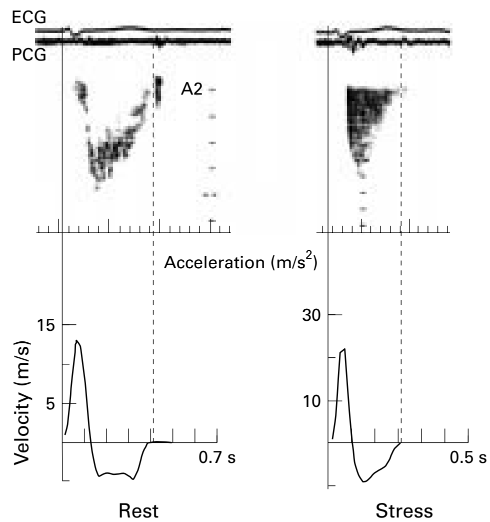

Figure 1 Measurements of peak aortic acceleration. Aortic Doppler and the corresponding digitised trace along with its first derivative.

Table 2 Doppler echocardiography and ECG reproducibility

Variable	*Intraobserver CV (%)*	*Interobserver CV (%)*
Z ratio (rest)	3.9	4.6
Z ratio (stress)	4.5	5.1
Aortic acceleration (rest)	3.7	4.0
Aortic acceleration (stress)	4.0	4.3
	Root mean square difference (ms)	*Coefficient of variation (%)*
QRS (rest)	2.7	2.5
QRS (stress)	3.3	3.2

CV, coefficient of variation.

Echocardiogram

Ventricular dimensions were measured using the minor axis M mode recording, from the leading edge of the septal endocardium to that of the posterior wall. Left ventricular end diastolic dimension was taken at the onset of the Q wave of the ECG, and end systolic dimension at the onset of the first high frequency vibration of the aortic component of the second heart sound on the phonocardiogram (A2). Fractional shortening was calculated as the percentage fall in left ventricular cavity dimension during systole with respect to that in diastole. Aortic velocity and left ventricular ejection and filling times were determined from the aortic and mitral Doppler tracings. Ejection time was measured as the interval between the onset of the forward flow pulse across the aortic valve to the onset of the aortic closure artefact. Filling time was measured from the onset of the E wave to the end of the A wave. Total ejection and filling periods were derived as the product of the corresponding time interval and heart rate, and expressed as seconds of ejection or filling per minute, respectively. The Z ratio was calculated from the sum of left ventricular ejection and filling times, divided by the RR interval, and expressed as a percentage.[3] Stroke distance was calculated as the time integral of aortic velocity, and stroke volume as the product of stroke distance and subaortic area. Aortic velocity traces

Table 3 Physiological effects of dobutamine stress in normal subjects and patients with coronary artery disease

	Control (n=17)		*Coronary artery disease (n=22)*	
Variable	*Rest*	*Stress*	*Rest*	*Stress*
Haemodynamics				
SD (cm)	13 (4)	18 (4)**	14 (4)	14 (4)‡
SV (ml)	70 (20)	90 (20)**	70 (20)	70 (20)‡
CO (l/min)	4.9 (1.4)	11.5 (2.5)**	5.2 (1.8)	8.5 (2.5)**‡
Mean BP (mm Hg)	102 (12)	101 (14)	107 (12)	100 (28)
PAA (G)	1.3 (0.3)	3.4 (0.6)**	1.3 (0.3)	2.8 (0.7)**†
Time intervals				
HR (beats/min)	76 (12)	119 (12)**	78 (14)	114 (18)**
QRS (ms)	91 (9)	87 (8)**	93 (14)	102 (18)**‡
LVET (ms)	266 (24)	183 (19)**	268 (33)	176 (21)**
LVET (s/min)	20 (3)	22 (2)*	21 (3)	20 (2)†
LVFT (ms)	383 (95)	275 (47)**	385 (110)	247 (60)**
LVFT (s/min)	28 (4)	33 (3)**	28 (4)	27 (3)‡
ET + FT (s/min)	48 (2)	55 (2)**	49 (3)	47 (4)**‡
Z ratio (%)	81 (4)	90 (4)**	82 (4)	78 (9)**‡

Values are means (SD).
*$p < 0.01$; **$p < 0.001$, stress *v* rest within group (paired *t* test).
†$p < 0.005$; ‡$p < 0.001$, stress values in patients with coronary artery disease *v* stress values in controls (unpaired *t* test).
BP, blood pressure; CO, cardiac output; HR, heart rate; LVET, left ventricular ejection time; LVFT, left ventricular filling time; PAA, peak aortic acceleration (1 $g = 9.81$ m/s^2); SD, stroke distance; SV, stroke volume.

were digitised off line (100 Hz) and the peak aortic acceleration rate in g (1 $g = 9.81$ m/s^2) was calculated from the first differential of the velocity trace with respect to time[4] (fig 1).

REPRODUCIBILITY

ECG and echocardiographic findings were analysed by two separate individuals, both blind to the original diagnosis. Intraobserver and interobserver variability was then assessed in 15 patients (with the third individual again blind to the original diagnosis). For QRS duration, duplicate ECG recordings were taken within one minute of each other. Paired ECGs were recorded at rest and at peak stress. Duplicate measurements of left ventricular ejection, filling, and RR intervals were used to assess the reproducibility of the Z ratio, while repeat digitisation of aortic velocity traces assessed the reproducibility of aortic acceleration. Within and between observer values were determined independently. Reproducibility was then expressed as the root mean square (RMS) difference between duplicate values, and the corresponding value of coefficient of variation as the ratio of RMS difference/mean value (table 2).

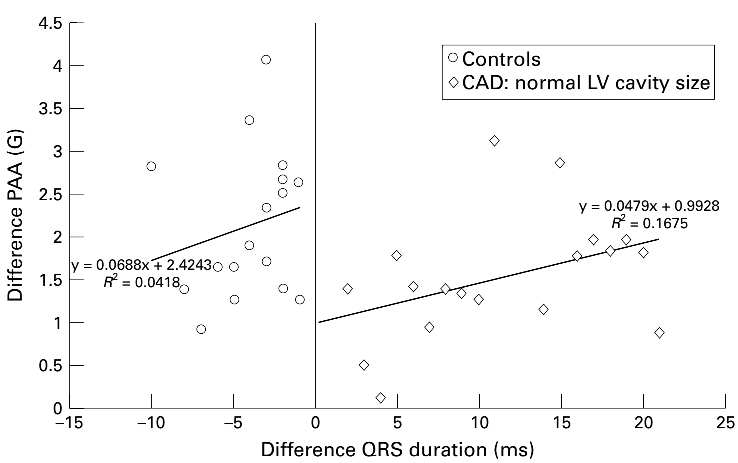

Figure 2 Relation between QRS and peak aortic acceleration. A plot to show the lack of correlation between difference in QRS duration and changes in peak aortic acceleration during dobutamine stress.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). Resting values were compared between controls and patients using Student's unpaired *t* test. Within control and patient groups, rest and stress values were compared using paired *t* tests. Correlation was performed by linear regression analysis. Incremental stress values in the controls and patients were compared by one way analysis of variance (ANOVA). A Bonferroni correction was applied for multiple comparisons and a significant difference was thus taken as $p < 0.01$.

Results

There was no age difference between patients and controls (table 1). The incidence of female subjects was higher in the control group, whereas the patient group was predominantly male. Ventricular dimensions in the ischaemic group were not different from controls, and myocardial infarction, hypertension, and diabetes were only present in the patient group.

In normal subjects, the end of stage 8 of the dobutamine protocol was taken as the stress end point, as none achieved target heart rate for age and none developed symptoms or ECG changes. In the patient group, target heart rate was not achieved in any patient. However, 17 developed chest pain (nine with ST elevation and eight with ST depression), while the remaining five were asymptomatic but developed T wave inversion. No test was terminated prematurely as a result of arrhythmia or hypotension.

HEART RATE AND QRS DURATION

Resting heart rate and QRS duration were similar in patients and controls (table 3). Heart rate increased significantly at peak stress in both groups, but QRS duration consistently shortened during stress in normal subjects (fig 2) by a mean of 4 ms, and increased by a mean of 9 ms with respect to resting values in patients with coronary artery disease (both $p < 0.001$).

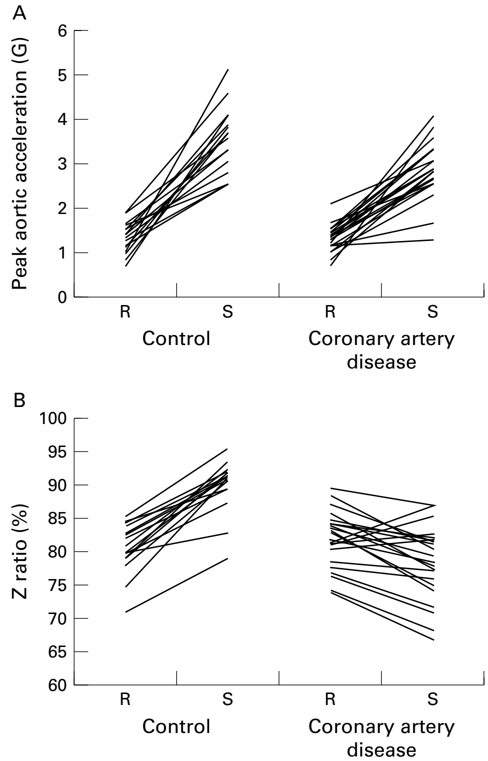

Figure 3 Effect of dobutamine on (A) peak aortic acceleration and (B) Z ratio. Individual subjects show positive inotropy with dobutamine, although the response is less striking in patients with coronary artery disease (R, rest; S, stress). Furthermore, the inotropic response is dissociated from changes in activation and Z ratio in patients with coronary artery disease.

STROKE VOLUME, CARDIAC OUTPUT, AND MEAN ARTERIAL PRESSURE

Stroke volume increased significantly in normal subjects but remained unchanged in patients at peak stress (table 3). Resting cardiac output was similar in controls and patients at rest. However, during stress, cardiac output increased by 135% in controls compared with 63% in patients ($p < 0.001$). Mean resting arterial pressure in patients was not different from controls, and remained unchanged with stress in both groups.

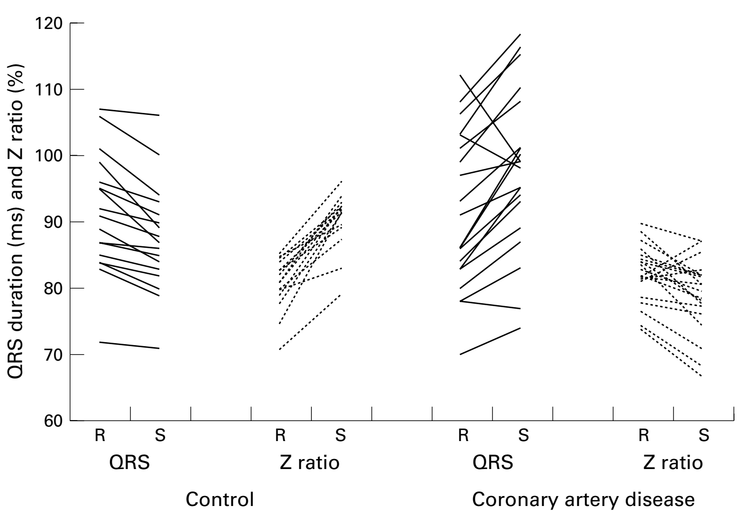

Figure 4 Effect of dobutamine on QRS duration and the Z ratio. As heart rate increases, QRS shortens and Z ratio increases in normal subjects. By contrast, in patients with coronary disease, QRS becomes prolonged and Z ratio falls. R, rest; S, stress.

AORTIC ACCELERATION

At rest, peak aortic acceleration in patients was not different from controls (table 3, fig 3). Although initial acceleration increased strikingly at peak stress in both groups ($p < 0.001$), the increase was greater in normal subjects (160%) than in those with coronary artery disease (115%, $p < 0.005$). QRS response did not correlate with the change in aortic acceleration in either group (fig 2).

LEFT VENTRICULAR EJECTION AND FILLING TIMES

Resting ejection and filling times were similar in control and patient groups, and as heart rate rose, both shortened significantly (table 3). In normal subjects, when the components of the cardiac cycle were analysed with respect to heart rate and expressed as seconds/minute, proportionately more time at rest was spent in filling the ventricle (28 s/min) than in ejection (20 s/min). During stress, total ejection period increased by 2 s/min ($p < 0.01$), which correlated with the increase in stroke volume ($r^2 = 0.71$). Total filling period increased by 5 s/min ($p < 0.001$), so that the total isovolumic period fell from 12 s/min at rest to 5 s/min at peak stress ($p < 0.001$). In patients with coronary artery disease, total ejection and filling periods were not different at rest from controls. Neither period increased during stress, and the total isovolumic period rose from 11 s/min to 13 s/min at peak stress ($p < 0.001$ compared with controls).

Z RATIO

In normal subjects, the Z ratio—which represents the fraction of the total RR interval during which the ventricle is either ejecting or filling—was 80% at rest and increased to a mean of 91% during stress ($p < 0.001$) (table 3). In individual patients, the extent of the increase in Z ratio correlated with the fall in QRS duration ($r^2 = 0.69$). By contrast, Z ratio fell during stress in patients with coronary artery disease from 82% to 78% ($p < 0.001$) as QRS duration increased ($r^2 = 0.65$) (fig 4). When normal subjects and patients were combined, the difference in Z ratio between rest and stress correlated with the extent of change of QRS duration ($r^2 = 0.72$) (fig 5).

SUBGROUP ANALYSIS

Subgroup analysis of patients with hypertension showed significant left ventricular hypertrophy (mean (SD) end diastolic septal thickness, 1.5 (0.3) cm *v* 0.9 (0.1) cm in controls; end diastolic posterior wall thickness, 1.3 (0.4) cm *v* 0.8 (0.2) cm in controls; both $p < 0.001$). However, neither the presence of resting left ventricular hypertrophy nor of diabetes was associated with significant differences in the Z ratio or peak aortic acceleration response in patients with coronary artery disease. Similarly, no differences were shown between patients receiving or not receiving angiotensin converting enzyme inhibitors or β blocking drugs.

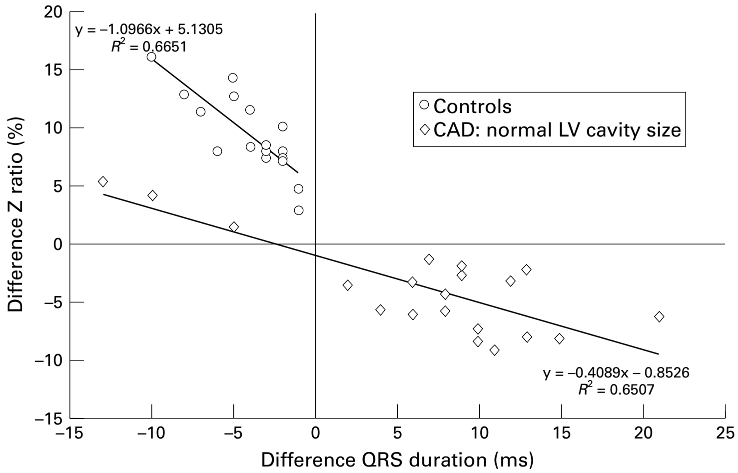

Figure 5 Plot showing the relation between QRS duration and the Z ratio in individual patients and controls combined. Normally, the greater the fall in QRS duration, the greater the increase in Z ratio. By contrast, QRS duration increases in patients during stress while the Z ratio falls.

Discussion

Traditionally, dobutamine stress echocardiography has been used to diagnose coronary artery disease, based on wall motion analysis.[5–7] However, recent studies have also shown a close association between ventricular activation and mechanical function during dobutamine stress.[2] With an understanding of the cardiovascular effects of dobutamine itself,[8] our aim was to assess the effect of activation on ejection and filling haemodynamics at rest and at peak stress, and to dissociate an impaired positive inotropic response from the effect of prolonged activation.

FINDINGS

Our results confirm that the normal haemodynamic response to dobutamine stress is an increase in cardiac output at constant arterial pressure. This change in output was mediated mainly by a rise in heart rate and, to a lesser extent, by an increase in stroke volume, which was in turn closely associated with an increase in the total ejection period at peak stress. At the same time, a powerful positive inotropic effect was demonstrated by an increase in the initial acceleration of blood into the ascending aorta. The effects of dobutamine stress on ventricular inflow were also clearly defined. Ventricular filling time per beat fell as the heart rate increased. However, total filling period per minute increased, and by a greater increment than the ejection period, so that the relative proportion of the cardiac cycle spent either ejecting or filling increased significantly at peak stress. Such is the effectiveness of the cardiac response to stress in normal subjects that only five seconds of every minute were spent in an isovolumic phase. The consistent shortening of the QRS duration at peak stress correlated closely with the increase in Z ratio (the proportion of the cardiac cycle either ejecting or filling) in individual patients.

These patterns were clearly modified in patients with coronary artery disease. Resting values of stroke volume, cardiac output, and peak aortic acceleration were similar to normal subjects. However, with the induction of ischaemia at high heart rates, QRS duration broadened, contrary to controls. Although left ventricular ejection and, in particular, filling times became shorter, both total ejection and filling periods failed to increase with stress. Consequently, for the same heart rate at peak stress, the ventricle was isovolumic for almost three times as long as in normal subjects. This difference in response to stress in patients with coronary artery disease could also be quantified by a fall in Z ratio at high heart rates. At the same time, stroke volume failed to increase in patients, so cardiac output was correspondingly lower and was purely rate related. Although peak aortic acceleration increased in both groups, it was lower than normal during stress in the patient group.

MECHANISMS

Our results suggest that dobutamine has at least two effects on the pattern of left ventricular contraction.

First, its well known positive inotropic effect—from stimulation of the β_1 receptors[9]—was demonstrated as an increase in initial aortic acceleration. Peak aortic acceleration has long been recognised as a sensitive index of ventricular inotropic state,[10–12] independent of loading conditions and changes in end diastolic volume. Its use in humans was initially explored by differentiating the velocity signal from a catheter tip flowmeter,[13] but its application was restricted by its invasive nature and low signal to noise ratio. However, initial acceleration can readily be derived non-invasively by differentiating the Doppler aortic flow velocity trace. In the present study, it proved very sensitive to the positive inotropic effects of dobutamine in normal subjects, and showed only minor attenuation in the presence of coronary artery disease.

The second effect of dobutamine in normal subjects was to prolong ejection and filling time per minute, and thus increase the Z ratio. In patients with coronary disease, exactly the opposite effect occurred: total ejection and filling periods failed to increase and the Z ratio consistently fell. In individual patients, these changes in Z ratio correlated closely with alterations in QRS duration, which became shorter in normal subjects and lengthened in those with coronary artery disease. Indeed, the level of correlation appeared to be limited mainly by the reproducibility with which the primary variables could be measured.[14] By contrast, changes in initial aortic acceleration showed no correlation at all with changes in QRS duration. We conclude, therefore, that the direct effect of dobutamine on the myocardium was reflected in changes in aortic acceleration, whereas alterations in the pattern of activation manifested themselves in terms of the relative intervals devoted to ejection and filling.

LIMITATIONS

In order to measure filling and ejection times, linear extrapolation to baseline was employed, as Doppler cannot detect zero flow. A digitisation frequency of 100 Hz may have led to underestimation of high values of aortic acceleration in control subjects, thus reducing differences between normal subjects and patients. Nevertheless, reproducibility expressed as coefficient of variability proved to be small, as it was for analysis of microprocessor determined ECG intervals, both within groups and for individual patients. The Z ratio differs from the Tei ratio,[15] which takes no account of the heart rate or filling time.

Three of 22 patients were receiving β blockers, but none required atropine to induce symptoms or ECG changes. Therefore, any overall β antagonistic effect was likely to be insignificant. In particular, these three patients were not the three in whom QRS duration fell with stress.

Although hypertension was present in a quarter of the patients, left ventricular hypertrophy did not affect the Z ratio or the peak aortic acceleration response. The aim of our study was not to analyse ischaemia induced wall motion. Thus the stress response of patients with coronary artery disease who do not develop definite ECG or classical echocardiographic evidence of inducible ischaemia remains unclear.

Finally, while it is tempting to equate the effects of dobutamine with exercise, we believe that this would be premature, as there are clear differences between the two. Nevertheless, the use of a pharmacological agent such as dobutamine, with a well documented haemodynamic profile, permits physiological investigation of the left ventricular response to increasing heart rate, cardiac output, and inotropic state under controlled conditions.

CONCLUSIONS

Our results thus show that the shortening of QRS duration that occurs during dobutamine stress in normal subjects and its prolongation in patients with coronary artery disease have predictable mechanical consequences in terms of altered left ventricular ejection and filling times. By contrast, the direct positive inotropic effect of dobutamine was manifest in both groups as an increase in peak aortic acceleration. It might have been predicted that a widened QRS duration would have led to asynchronous contraction and thus to a fall in aortic acceleration, but this did not prove to be the case. Our inability to demonstrate this interaction illustrates the degree to which the activation change and direct myocardial stimulation were dissociated by the methods we used. We believe that altered activation, and the associated changes in ejection and filling times, may contribute to the normal response to physiological as well as pharmacological stress, and to its impairment in patients with coronary artery disease. Furthermore, our results confirm previous suggestions[3] that changes in ventricular activation primarily alter time intervals within the cardiac cycle, particularly those reflecting the balance between ejection and filling times on the one hand and isovolumic periods on the other, rather than measurements of inotropic state.

We believe that further studies of these electromechanical effects are warranted to understand the normal response to dobutamine stress, to elucidate mechanisms underlying impaired ventricular performance in disease, and to optimise pacemaker function when this approach is used as a means of treating patients with heart failure and abnormal activation.

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